Towards Reliable Early Diagnosis of Diabetic Cardiac Autonomic Neuropathy using Complexity features of ECG

*Sridhar P Arjunan[a], Sharanya S[b]

ABSTRACT

Cardiac Autonomic Neuropathy (CAN) is a serious and often underdiagnosed complication of diabetes mellitus, associated with a markedly increased risk of cardiovascular morbidity and mortality. The asymptomatic nature of early-stage CAN presents substantial challenges in clinical detection and timely intervention. This study introduces an integrated framework combining advanced signal processing and machine learning techniques for the early diagnosis of CAN using electrocardiogram (ECG) signals. Temporal dynamics of ECG segments were analyzed using Fractal Dimension and entropy-based measures to capture subtle perturbations in autonomic modulation. A hybrid diagnostic system encompassing both hardware acquisition and software analytical modules was developed, enabling robust, real-time assessment of cardiac autonomic function. Convolutional neural networks (CNNs) and fully connected neural networks (NNs) were employed for automated classification, achieving high diagnostic accuracy. The developed ECG-CAN device, incorporating these analytical techniques, has been provisionally patented, underscoring its innovation and translational potential. This approach demonstrates enhanced sensitivity and reliability for early CAN detection, paving the way for proactive risk management in diabetic populations.

*Corresponding Author:

*[a] Research Fellow, School of Engineering,
RMIT University,
Melbourne, Australia*

*[b] Department of Electronics and Instrumentation Engineering,
SRM Institute of Science and Technology, Kattankulathur,
Chennai, INDIA*

INTRODUCTION

Electrocardiography (ECG) is a widely utilized, non-invasive diagnostic method for assessing the electrical activity of the heart throughout the cardiac cycle. It records voltage variations as a function of time, producing an electrocardiogram that reflects cardiac conduction dynamics. The primary purpose of ECG recording is to obtain detailed information about the electrical performance and physiological status of the myocardium. Conventionally, a standard 12-lead ECG is employed, allowing assessment of the heart's electrical activity from twelve distinct spatial orientations over a defined recording period (Peura, 2020).

During each cardiac cycle, a healthy heart exhibits a sequential pattern of depolarization initiated by pacemaker cells in the sinoatrial node. The excitation propagates through the atria, traverses the atrioventricular node, and continues along the bundle of His and Purkinje fibers, leading to ventricular depolarization directed downward and leftward (Hall, 2020). This orderly propagation produces the characteristic ECG waveform. To trained clinicians, ECG signals convey extensive diagnostic information regarding cardiac rhythm, chamber dimensions, myocardial integrity, conduction abnormalities, pharmacological effects, and pacemaker function (Gehlen, 2020).

Modern ECG systems consist of multiple electrodes interfaced with a central processing unit. While earlier ECG devices employed analog circuitry, contemporary systems incorporate analog-to-digital converters (ADCs) to transform cardiac electrical signals into digital form. Recent technological advancements have led to the development of compact, portable ECG devices with integrated displays and wireless data transmission capabilities. Additionally, wearable ECG sensors integrated into fitness trackers and smartwatches enable real-time, single-lead monitoring using minimal electrode configurations (Hamilton, 2002).

ECG analysis plays a vital role in the management of diabetic patients, who are at elevated risk for cardiovascular complications such as coronary artery disease, arrhythmias, and silent myocardial ischemia. Continuous or periodic ECG monitoring enables early detection of subclinical abnormalities, supporting timely therapeutic interventions and improved cardiovascular outcomes in diabetic populations (Stern, 2009). Recent studies have demonstrated strong associations between reduced HRV, ECG complexity alterations, and increased cardiovascular morbidity in diabetes, underscoring the unmet need for early detection of CAN (Kim et al., 2025; Raje et al., 2025).

Diabetes Mellitus and Its Complications

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion or utilization. The global diabetic population has surpassed 500 million and continues to rise. Long-term diabetes leads to several complications, notably neuropathies affecting peripheral and autonomic systems. Cardiac Autonomic Neuropathy (CAN), a severe autonomic complication, arises from chronic hyperglycemia-induced damage to autonomic nerve fibers regulating cardiac function (Gehlen, 2020). While traditionally linked to long-standing diabetes, CAN is now recognized to manifest in early or prediabetic stages, expanding its clinical significance (Hamilton, 2002). Recent findings suggest that Cardiac Autonomic Neuropathy can occur even in early diabetes stages and may be detectable through subtle ECG signal changes and reduced autonomic modulation (Chen et al., 2025; Raje et al., 2025).

Clinical Significance of CAN

CAN is among the most underdiagnosed yet life-threatening complications of diabetes. It impairs autonomic regulation of cardiovascular activity, producing symptoms such as resting tachycardia, exercise intolerance, arrhythmias, and silent myocardial infarctions. In advanced cases, it contributes to increased mortality and sudden cardiac death. Diagnosis conventionally relies on the Ewing battery of cardiovascular reflex tests, the current clinical gold standard. However, these tests are time-intensive and impractical for large-scale screening, prompting exploration of ECG-based, non-invasive diagnostic alternatives (Stern, 2009). Contemporary research strongly supports the utility of HRV indices, coherence measures, and ECG-derived nonlinear features as early biomarkers of CAN (Braffett et al., 2025; Chen et al., 2025).

Importance of Early Diagnosis

Early detection of CAN is critical to prevent progression and enable timely therapeutic interventions. Its asymptomatic onset often delays diagnosis. Recent studies highlight ECG-based

analysis as an accessible, low-cost tool for early detection. Specific ECG intervals—PR, QT, RR, and ST—show measurable deviations in CAN patients. Advanced analytical approaches incorporating complexity measures such as Fractal Dimension (FD) and entropy, combined with machine learning models including Convolutional Neural Networks (CNNs), have achieved promising diagnostic accuracy (Sharanya, 2023). AI-based classification models and multifractal ECG features have further demonstrated early detection potential (Nabrdalik et al., 2024; Singh et al., 2024).

Objectives

The primary objective of this study is to develop an advanced, reliable, and clinically applicable framework for the early detection of Cardiac Autonomic Neuropathy (CAN) using electrocardiogram (ECG) signals. Specifically, the study aims to quantify the temporal and nonlinear complexity of ECG segments using Fractal Dimension and entropy-based features to capture subtle autonomic dysregulation often missed in conventional analyses. A further objective is to design and implement a hybrid hardware–software diagnostic system capable of real-time ECG acquisition and automated assessment. This includes the development and evaluation of machine learning models—particularly convolutional neural networks (CNNs) and fully connected neural networks (NNs)—to classify CAN with high sensitivity and specificity. Additionally, the study seeks to translate these analytical techniques into a functional prototype ECG-CAN diagnostic device, which has been provisionally patented, to demonstrate the feasibility of deploying the proposed methods in practical clinical environments.

PATHOPHYSIOLOGY AND RISK FACTORS OF CAN

Mechanisms of Autonomic Dysfunction in Diabetes

The development of CAN is primarily driven by chronic hyperglycemia, which triggers oxidative stress, protein kinase C activation, polyol pathway alterations, and accumulation of advanced glycation end-products (AGEs). These processes lead to microvascular damage, neuronal apoptosis, and axonal degeneration (Sharanya, 2021). Early-stage CAN involves vagal nerve damage, causing

parasympathetic dysfunction and reduced heart rate variability (HRV). As progression occurs, sympathetic fibers are also affected, leading to orthostatic hypotension and arrhythmias. ECG manifestations such as QT prolongation, ST depression, and PR segment alterations provide clinical indicators of disease severity (Cryer, 2005).

Established and Emerging Risk Markers

Duration of diabetes, poor glycemic control, age, hypertension, dyslipidemia, and obesity are established risk factors for CAN. Prevalence ranges from 2–90% in type 1 and 25–75% in type 2 diabetes and can occur even in prediabetes. Emerging biomarkers—such as high-sensitivity cardiac troponin, ST2, GDF-15, and NT-proBNP—are being explored for earlier detection. Signal complexity measures, including FD and entropy applied to ECG segments, have shown strong potential for differentiating CAN-positive and healthy subjects, with neural network classifiers achieving accuracies exceeding 84% (Serhiyenko, 2018).

Clinical Challenges in Diagnosing CAN

Despite its significance, CAN remains under diagnosed due to nonspecific symptoms, lack of standardized criteria, and limited accessibility to specialized testing. Cardiovascular autonomic reflex tests (CARTs) remain the diagnostic benchmark but require trained personnel and controlled environments (Senthamilselvan, 2022). Short-term ECG-based HRV analysis provides a practical alternative, with reduced high-frequency components indicating parasympathetic dysfunction (Pappachan, 2008). Recent translational research focuses on combining software-based analytical techniques with hardware implementations using microcontroller boards for real-time CAN detection. However, limited awareness, absence of unified treatment protocols, and variability in diagnostic interpretation continue to hinder early diagnosis (Hlatky, 2009).

ELECTROCARDIOGRAM AS A DIAGNOSTIC TOOL FOR CARDIAC AUTONOMIC NEUROPATHY

The Electrocardiogram (ECG) remains one of the most widely utilized non-invasive diagnostic modalities for assessing cardiac electrical activity and autonomic regulation. By graphically representing the heart's depolarization and repolarization patterns,

ECG signals provide valuable insights into the timing, rhythm, and morphology of cardiac cycles. Key components such as the P wave, QRS complex, and T wave, along with intervals including PR, QT, RR, and ST, correspond to distinct electrophysiological phases and are sensitive to autonomic modulation. Within the context of autonomic function, ECG serves as an essential tool for evaluating the interplay between sympathetic and parasympathetic branches of the autonomic nervous system (ANS).

Heart rate variability (HRV), derived primarily from RR interval fluctuations, represents a critical marker of autonomic tone, with reductions in HRV—especially in the high-frequency domain—signifying parasympathetic impairment and early subclinical stages of Cardiac Autonomic Neuropathy (CAN). Parameters such as prolonged QT intervals and variations in PR and ST segments further reflect autonomic imbalance induced by chronic hyperglycemia in diabetic patients. Modern approaches employing nonlinear dynamics, including fractal dimension (FD) and entropy analysis, have enhanced ECG-based assessments by detecting subtle, nonlinear signal complexities often overlooked by conventional HRV measures (Pappachan, 2008).

CAN induces progressive and quantifiable alterations in ECG morphology and time-domain intervals, reflecting the deterioration of autonomic nerve control over cardiac activity. The earliest and most consistent manifestation is decreased HRV, followed by resting tachycardia resulting from parasympathetic withdrawal and sympathetic predominance. Morphological abnormalities, including QT interval prolongation and ST segment depression, indicate myocardial ischemia and heightened risk of arrhythmias and sudden cardiac death. PR interval variations often accompany these changes, correlating with disease severity and conduction abnormalities.

Recent translational research employing FD and entropy-based analyses demonstrates significant distinctions in ECG interval complexity—particularly in PR and QT segments—between healthy individuals and those with both early and definite CAN (Imam, 2015). These findings have been validated in simulated and clinical ECG datasets, with hardware implementations confirming lower error rates for PR and QT segments, underscoring their potential in real-time diagnostic applications

(Sharanya, 2023). Furthermore, machine learning techniques, notably Convolutional Neural Networks (CNNs), have achieved high accuracy in classifying CAN using fractal and entropy-derived ECG features, establishing a promising foundation for automated, non-invasive, and scalable diagnostic systems.

MATERIAL AND METHODS

The efficacy of electrocardiogram (ECG)-based diagnostics, particularly in the identification of autonomic dysfunctions such as Cardiac Autonomic Neuropathy (CAN), is significantly influenced by advanced signal processing techniques. Given the delicate nature of ECG recordings and their susceptibility to various interpretations, sophisticated analytical methodologies are essential for extracting meaningful diagnostic data. In contemporary research, a combination of preprocessing, feature segmentation, fractal geometry analysis, and entropy-based complexity measures is frequently employed to discern subtle abnormalities in cardiac electrical activity, particularly those associated with CAN.

Preprocessing and Segmentation of ECG signals

Raw ECG signals often contain undesired components such as baseline fluctuations, muscular artifacts, motion-induced noise, and electrical interference from external sources. These distortions can obscure vital morphological features and introduce errors in detecting important cardiac events. As a result, preprocessing is a necessary initial step to improve signal quality and reliability before further analysis. Typically, baseline wander caused by patient movement or breathing, is removed using high pass filters with cutoff frequencies ranging between 0.5Hz to 3Hz. Power line interference, a common issue due to ambient electrical fields, is eliminated using a notch filter, often set at 50 Hz or 60 Hz depending on regional power standards. And band-pass filtering within the range of 3-40 Hz is frequently applied to preserve the diagnostic features of the ECG while suppressing high-frequency noise.

Followed by signal cleaning, segmentation involves identifying specific features of the ECG waveform, such as P, QRS, and T waves, R-peak detection is particularly important, as it serves as a reference for calculating intervals like RR, QT, PR, and ST segments. Algorithms like Pan-Tompkins,

Hamilton, and derivative-based thresholding methods are commonly used for reliable peak detection. Accurate segmentation is crucial because autonomic regulation influences the duration and variability of these intervals, and abnormalities within them can reflect early signs of CAN or other cardiac dysfunctions.

In advanced studies, segmentation extends beyond detecting fixed points to analyze patterns within specific ECG segments over time. This enables researchers to capture dynamic variations in signal morphology, which are valuable in assessing progressive conditions like CAN where subtle changes accumulate over continuous monitoring.

Fractal Dimension Analysis of ECG Time Segments

Fractal Dimension (FD) analysis provides a sophisticated approach to assessing the irregularity and complexity of biological signals, such as electrocardiograms (ECGs). Unlike linear methods that assume stationarity and uniformity in signal patterns, FD captures the inherent self-similarity and complexity found in physiological systems. This makes it particularly effective for identifying nuanced variations associated with autonomic neuropathies.

FD quantifies the geometry intricacy of time series data, providing a numerical value that reflects the signal complexity. Higher FD values generally indicate more intricate, irregular patterns, whereas lower values suggest a simpler, more predictable structure. This property is especially useful for detecting early autonomic dysfunctions, as the electrical activity of the heart becomes less variable and more uniform in response to impaired autonomic control.

Multiple algorithms exist for calculating FD, including box-counting, Higuchi's, Petrosian's, and Katz's methods. Each method varies in computational complexity and sensitivity to specific signal features. For example, the box-counting technique estimates FD by covering the signal with grids of varying sizes and counting the number of boxes containing parts of the signal. Higuchi's method, on the other hand, evaluates FD by analyzing the length of the signal curve over different time intervals, offering better resolution for short, non-stationary data segments, such as those found in ECG recordings.

In CAN-related research, FD has been applied to key ECG intervals, including RR, QT, PR, and ST segments. Studies consistently demonstrate that FD values derived from these segments differ significantly between healthy individuals and those with early or established CAN. These findings confirm that FD analysis effectively captures autonomic disturbances undetectable by conventional heart rate variability (HRV) analysis alone, supporting its integration into early diagnostic protocols.

Models of neural networks for CAN input classification

Contemporary data analysis methodologies, particularly neural networks, exhibit exceptional efficacy in the analysis of spatial data (Gogan, 2025). Presently, it stands as the most expedient analysis technique for pixel data, contingent upon meticulous data preprocessing and processing. This method has demonstrated superior accuracy compared to conventional analysis approaches. Figure 1 delineates the three fundamental neural network models utilized for the CAN classification.
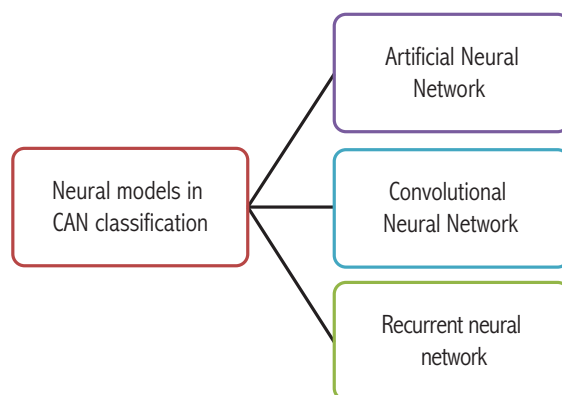
**Figure 1** Neural Network models used for CAN classification

Artificial Neural network (ANN): Artificial Neural Networks (ANNs) have been extensively investigated for their potential in classifying Cardiac Autonomic Neuropathy (CAN) due to their capacity to model nonlinear relationships between input features and diagnostic outcomes. Typically, these models utilize pre-extracted features from RR interval data, including time-domain and frequency-domain heart rate variability (HRV) metrics (Garruti, 2012). However, the feasibility of ANNs has diminished due to their inefficiency in processing complex data sets and their limited scalability. Additionally, ANNs necessitate more manual intervention in classification and analysis processes.

Recurrent Neural Network (RNN): In the analysis of Cardiac Autonomic Neuropathy (CAN), Recurrent Neural Networks (RNNs) are employed to model the temporal behavior of RR intervals derived from electrocardiogram (ECG) signals. These networks process the RR interval sequence sequentially, utilizing their internal memory to retain information about preceding intervals. This characteristic renders RNNs highly suitable for capturing the dynamic fluctuations in heart rate variability, which are often indicative of autonomic dysfunction. By learning patterns across time, RNNs can discern subtle, progressive alterations in autonomic control, thereby enabling more accurate classification of CAN severity.

Convolution Neural Network (CNN): Despite the drawbacks associated with the aforementioned techniques, Convolution Neural Network (CNN) possesses the capability to process non-linear and intricate data with exceptional precision and practicality. It comprises a series of layers, each of which is individually responsible for the processing and manipulation of data (Hayne, 2021). The comprehensive architecture of the CNN architecture for the CAN classification is elucidated in the subsequent section.

Architecture of Convolution Neural Network (CNN)

Figure 2 depicts the distinct layers of CNN architecture employed in the diagnostic model for ECG feature analysis in CAN diagnostic devices. These features, including patterns and shapes, are crucial for identifying the "RR" peaks, which are essential for CAN classification.
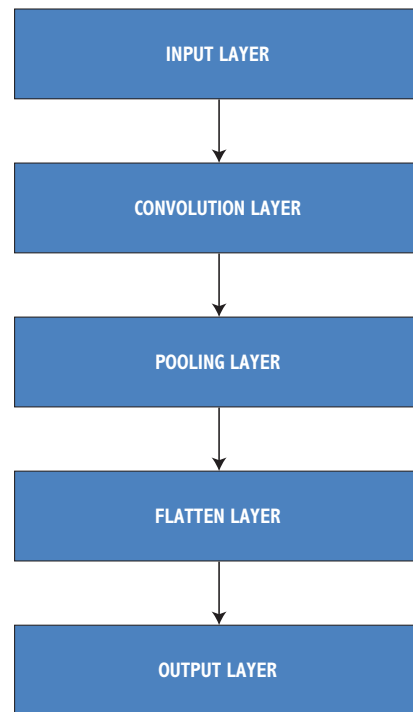
Figure 2 Layers of the CNN architecture

Input Layer: The ECG signal, acquired for a duration of 20 minutes with intermittent breaks, serves as the input to the neural network. Each pixel within the 2D image represents the signal strength at a specific time and the heartbeats. Properly formatting the input data ensures that the subsequent Convolution layers can effectively extract pertinent spatial and temporal patterns essential for accurate cardiac autonomic classification. The input layer does not perform computations itself but acts as a placeholder to provide the network with consistent, normalized data.

Convolution Layer: The Convolution layer is the primary layer of CNN architecture in which the input pixel data is filtered to derive signals with specific RR peaks that are necessary for CAN classification. A low-pass filter frequency of 45 Hz is applied to eliminate high-frequency noise in the input signal. This layer is instrumental in capturing local patterns, such as the interval between the peaks and minor variations in the ECG wave signals (Liu, 2013).

Pooling Layer: After the signal is filtered and processed, it undergoes activation function application for output determination. In this analysis of CAN segmentation, the ReLU activation function is employed for enhanced precision. The pooling layer

facilitates the reduction of the processed data's size and summarizes the precise requirements from the input graph. By minimizing the size, the network becomes faster and more resilient to handle intricate input signals. During the initial iteration, the layer identifies the patterns of the RR peaks, and in subsequent analyses, it comprehends the patterns and variations in the RR peak values.

Flatten Layer: The Flatten layer transforms the 2D processed ECG signal data into a 1D vector for matrix calculations and classification. It processes

the extracted features and associated patterns with predefined classifications, such as severe CAN, Early CAN, etc.

Output Layer: The output layer of a convolution neural network is responsible for delivering the final classification results based on the features extracted by the preceding layers. In the context of cardiac autonomic classification, this layer typically comprises one or more neurons corresponding to the number of diagnostic categories, such as normal, early CAN, and definite CAN.

Figure 3 illustrates the complete workflow of the CNN architecture, which enables the automatic learning of spatial features from ECG data and classification of the CAN groups.
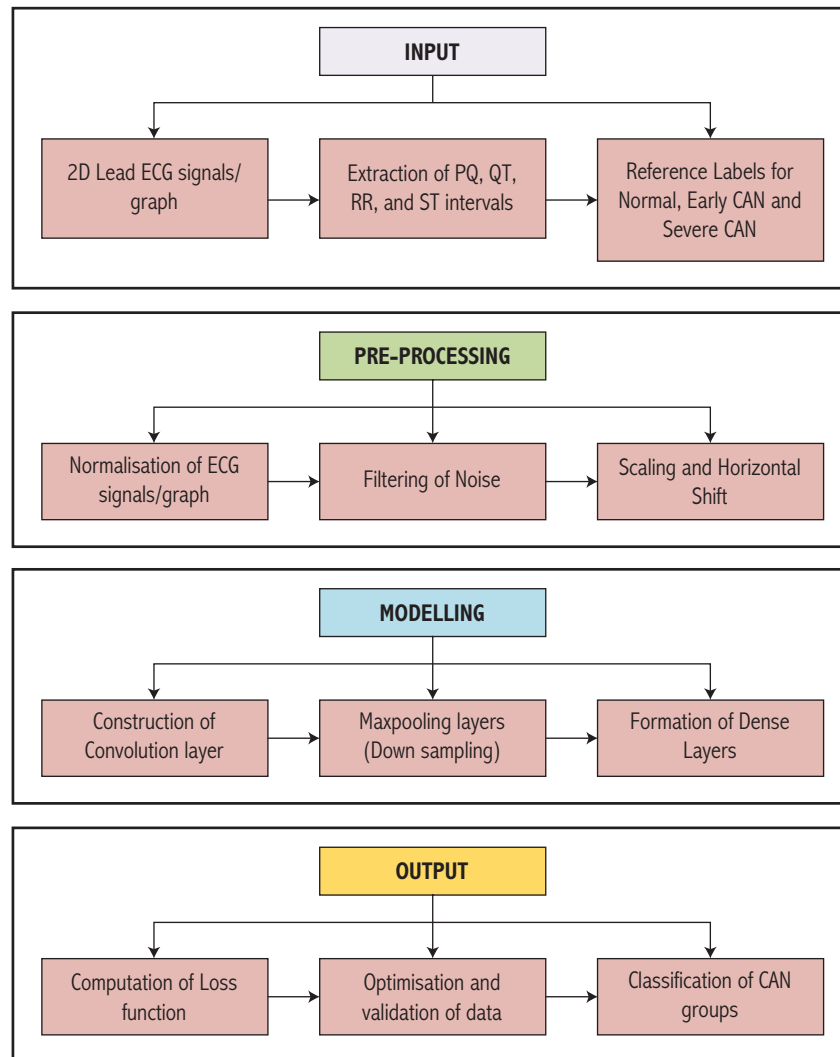
Figure 3 Workflow of the CNN architecture for CAN classification

Performance metrics – Classification accuracy and sensitivity

To evaluate the entire neural network architecture, two generalized categories that are primarily responsible for biomedical classification is considered – Classification accuracy and classification sensitivity. Classification accuracy reflects the proportion of all correctly identified instances, both positive and negative, over the total number of cases. Similarly, classification sensitivity refers to the minimal change that can be detected by the neural network.

RESULTS AND DISCUSSION

Signal Acquisition Systems

The ECG signal was acquired and processed through the following steps:

Step 1: Signal Acquisition

The Electrocardiogram (ECG) signals were acquired using the Biopac MP36 data acquisition system, a widely utilized platform for physiological signal recording and analysis. A standard Lead-II configuration was employed, with three electrodes positioned on the right arm, left leg, and right leg

(ground). The ECG was recorded at a high sampling rate of 1000 Hz to ensure precise capture of waveform details, particularly in the RR intervals and other cardiac cycle segments critical for autonomic assessment. Each recording session lasted 20 minutes, providing sufficient data for robust analysis (Cornforth, 2011).

Step 2: Filtering

The acquired signals were filtered using a 3–45 Hz bandpass filter to eliminate baseline wander and high-frequency noise, along with a notch filter to eliminate powerline interference.

Step 3: Segmentation

The clean ECG signals were then segmented into 5-minute windows and further processed to extract PR, QT, RR, and ST intervals. These segments were subsequently transformed into 2D representations for CNN-based classification, enabling the model to learn morphological and temporal features associated with various stages of Cardiac Autonomic Neuropathy (CAN). Figure 4 presents the results obtained from ECG time segments for different CAN groups.
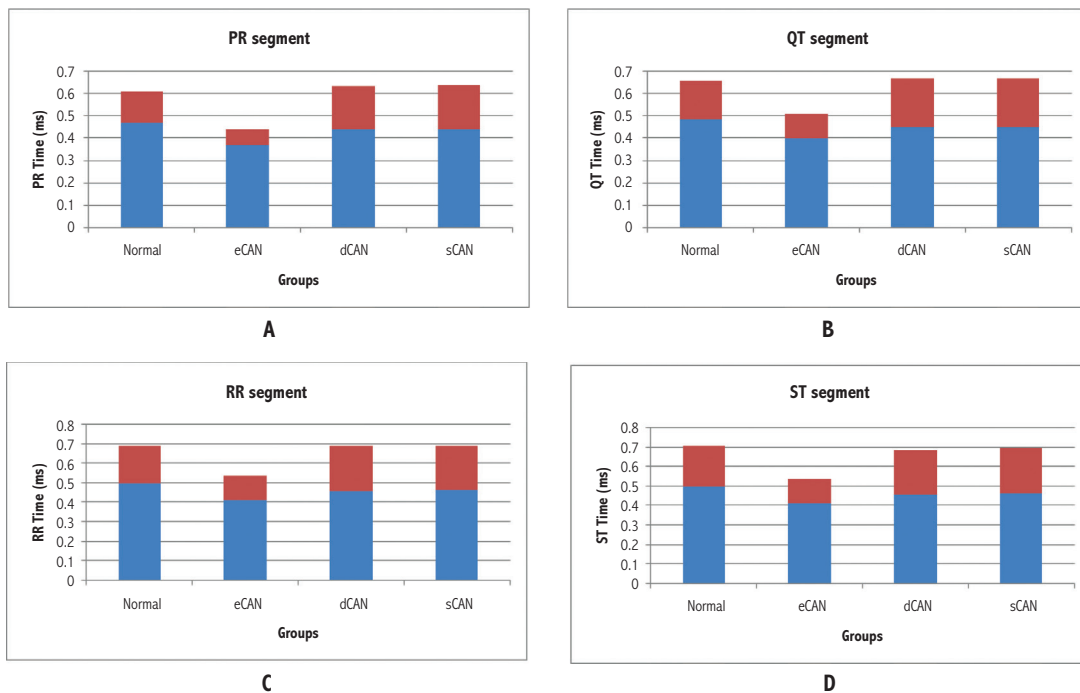

Figure 4 Mean and SD value for different ECG segments a) PR segment b) QT segment c) RR Segment d) ST segment

For the hardware implementation, a Sony Spresence controller is utilized for the device. The three electrodes, attached to the ECG leads, are connected to the ECG sensor. The Spresence extension is responsible for transmitting the bio-potential level of the body in the form of analog input to the controller board. This controller is connected to the ESP01 WIFI module to facilitate wireless connection between the computer and the hardware device. Figure 5 illustrates the components utilized for the device and the final prototype model.

ECG segment for individual subjects (Jun, 2018). These statistical measures were used to assess the variability in segment complexity and to distinguish between Normal, Early CAN, Definite CAN, and Severe CAN cases. Python's robust numerical analysis capabilities, including matrix operations and signal visualization, made it ideal for both statistical interpretation and graphical representation of the CNN results. This integration ensured consistency in data handling across the workflow and provided a reliable environment for evaluating the diagnostic output of the model.
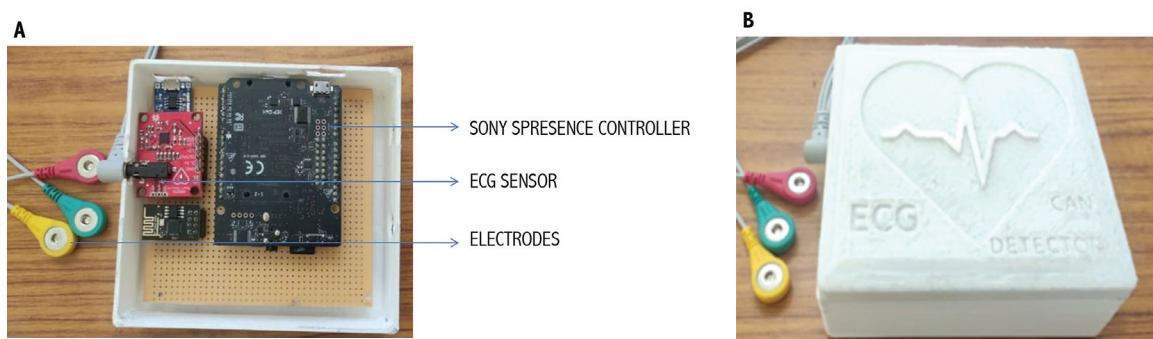

Figure 5 a) ECG Hardware CAN Diagnosis device b) Front cover of the ECG CAN diagnosis device (PROVISIONAL PATENTED)

### Integration with software tools

In this study, Python was employed as the primary computational platform to facilitate various stages of ECG signal analysis and CNN-based classification of Cardiac Autonomic Neuropathy (CAN). Following the preprocessing and segmentation of ECG signals into physiologically relevant intervals (PR, QT, RR, and ST), MATLAB (2022b) was utilized to implement core functions for feature extraction, image transformation, and data preparation suitable for CNN input. After CNN processing, MATLAB (2022b) was utilized to compute the mean and standard deviation of the CNN output readings—specifically the fractal dimension (FD) values derived from each

Across all segments, there is a clear trend where FD values tend to increase progressively from the Normal group to the Severe CAN group (as shown in Figure 6), particularly in the RR and ST segments. This indicates a higher degree of signal complexity and irregularity in patients with advanced stages of CAN. The QT segment shows relatively stable FD values with moderate separation among classes, while the PR segment demonstrates less variation across all groups, suggesting it may be less sensitive to CAN progression in this analysis. The standard deviation bars indicate variability within each class, especially in the Severe CAN group, likely due to the physiological inconsistency associated with autonomic dysregulation.

A

B

C

D
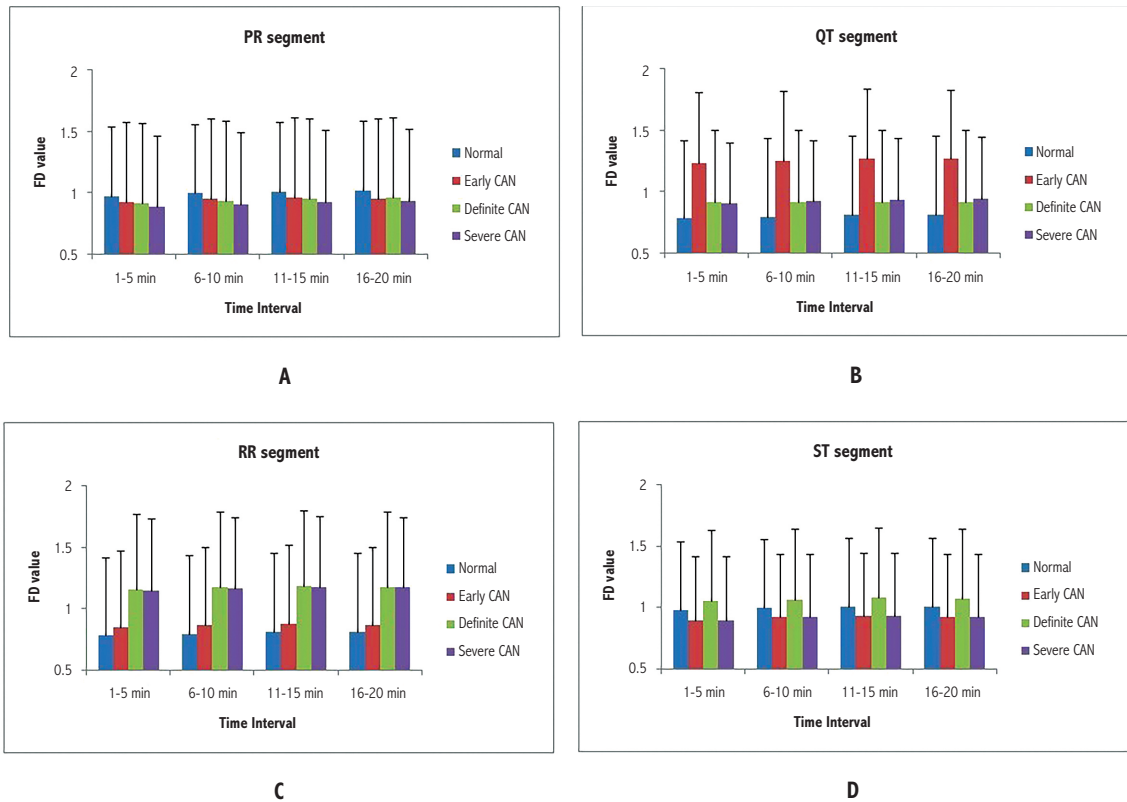
Figure 6 Mean and Standard Deviation of FD for the CAN data of the a) PR segment, b) QT segment, c) RR segment, d) ST segment for every 5min-interval

Figure 7 and Figure 8 depict the output graphs of the filtered signal and the CAN classification, respectively. Table 1.1 presents the accuracy and sensitivity values for individual sectors in the CAN analysis.
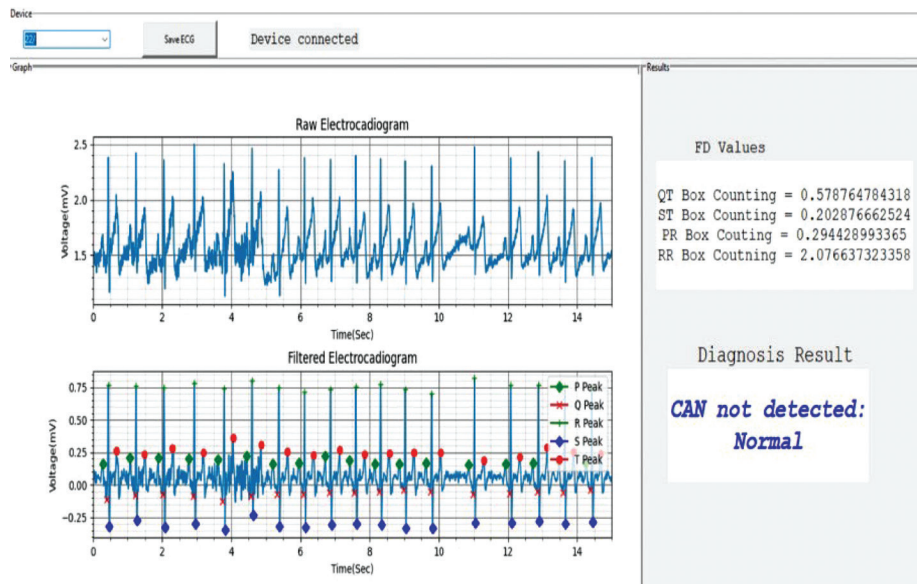
Figure 7 Output demonstrating the diagnosis of a normal individual.
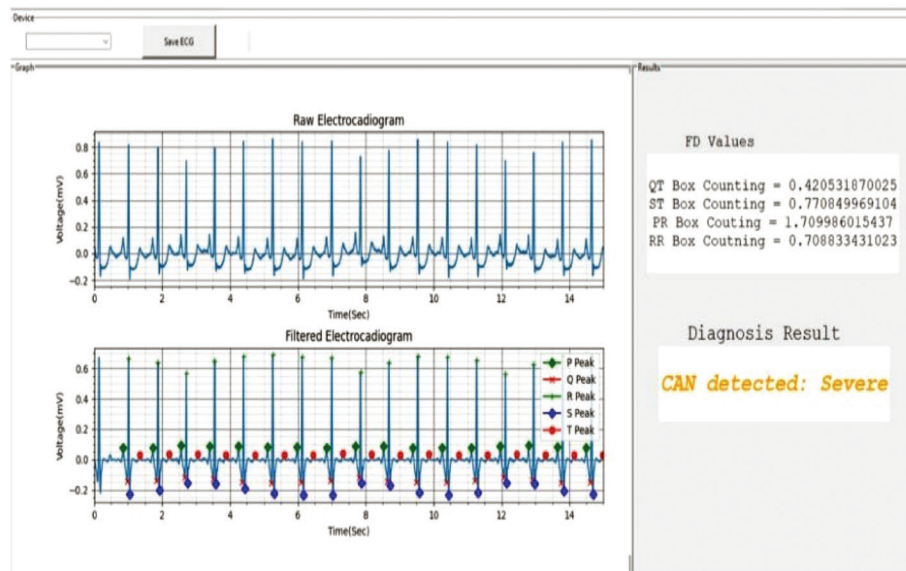
Figure 8 Output demonstrating the diagnosis of a severe case of CAN

Table 1.1 Accuracy and sensitivity of the data

CAN STAGE	ACCURACY	SENSITIVITY
Early CAN(e-CAN)	95%	97%
Definite CAN	93%	95%
Severe CAN	91%	92%

In summary, the RR and ST segments demonstrated the most significant differentiation between classes, rendering them particularly advantageous for classification tasks utilizing convolutional neural networks (CNNs).

CONCLUSION

This study demonstrated the efficacy of a Convolutional Neural Network (CNN) in classifying Cardiac Autonomic Neuropathy (CAN) by analyzing the fractal complexity of segmented electrocardiogram (ECG) signals, particularly across the PR, QT, RR, and ST intervals. The model successfully distinguished between Normal, Early, Definite, and Severe CAN stages, with RR and ST segments exhibiting the most significant complexity shifts in accordance with the severity of autonomic dysfunction. The findings emphasize the value of CNNs in detecting subtle waveform anomalies, providing a reliable, non-invasive tool for early CAN diagnosis. As manual interpretation of ECG remains constrained by variability and clinical workload, deep learning models such as CNNs offer a scalable and efficient solution. In the future, the integration of multimodal physiological data, including blood pressure variability, respiration, and skin conductance, may further enhance classification accuracy. Additionally, future advancements may encompass hybrid deep learning models (e.g., CNN-LSTM), deployment of real-time wearable monitoring systems, and expansion of datasets to encompass larger, more diverse populations for improved generalizability. These directions hold promise for more comprehensive and personalized assessments of autonomic dysfunction. The findings align with prior research supporting artificial intelligence-based approaches for cardiovascular risk prediction and reinforce the clinical utility of deep learning in autonomic neuropathy detection.

Conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

REFERENCES

Acharya, R., Faust, O., Kannathal, N., Chua, T., & Laxminarayan, S. (2005). Non-linear analysis of EEG signals at various sleep stages. *Computer methods and programs in biomedicine,* 80(1), 37-45.

Anastasiou, D., & Bantekas, I. (2023). Education for learners with disabilities as a social right. *U. Pa. J. Const. L.,* 25, 365.

Braffett, B. H., El Ghormli, L., Martin, C., Kewalramani, R., Tamborlane, W. V., Marcovina, S. M., (2025). Cardiovascular autonomic neuropathy defined by indices of heart rate variability is associated with cardiovascular disease in patients with type 1 diabetes. *Cardiovascular Diabetology,* 24, Article 15.

Chen, Y.-C., Liu, W.-M., Liu, H.-R., Tsai, C.-F., Wu, H.-T., & Kuo, T. B. (2025). Coherence analysis of cardiovascular signals for detecting early diabetic cardiac autonomic neuropathy with different glycated hemoglobin levels. *Diagnostics,* 15(12), 1474.

Clifford, G. D., & Azuaje, F. (2006). Advanced methods and tools for ECG data analysis (Vol. 10). *P. McSharry (Ed.). Boston: Artech house.*

Cornforth, D.; Jelinek, H.F.; Tarvainen, M. A comparison of nonlinear measures for the detection of cardiac autonomic neuropathy from heart rate variability. *Entropy* 2015, 17, 1425–1440.

Cryer, P. E. (2005). Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. *Diabetes,* 54(12), 3592-3601.

Garruti, G., Giampetruzzi, F., Vita, M. G., Pellegrini, F., Lagioia, P., Stefanelli, G., ... & Giorgino, F. (2012). Links between metabolic syndrome and cardiovascular autonomic dysfunction. *Journal of Diabetes Research,* 2012(1), 615835.

Gehlen, H., Faust, M. D., Grzeskowiak, R. M., & Trachsel, D. S. (2020). Association between disease severity, heart rate variability (HRV) and serum cortisol concentrations in horses with acute abdominal pain. *Animals,* 10(9), 1563.

Gogan, A., Potre, O., Avram, V. F., Andor, M., Caruntu, F., & Timar, B. (2025). Cardiac autonomic neuropathy in diabetes mellitus: pathogenesis, epidemiology, diagnosis and clinical implications: a narrative review. *Journal of Clinical Medicine,* 14(3), 671.

Hall, J. E., & Hall, M. E. (2020). Guyton and Hall Textbook of Medical Physiology E-Book: *Guyton and Hall Textbook of Medical Physiology E-Book. Elsevier Health Sciences.*

Hamilton, P. S. (2002). A comparison of adaptive and nonadaptive filters for reduction of power line interference in the ECG. *IEEE transactions on biomedical engineering,* 43(1), 105-109.

Hayne, L., Clyne, J., & Li, S. (2021, December). Using neural networks for two dimensional scientific data compression. In 2021 *IEEE International Conference on Big Data (Big Data)* (pp. 2956-2965). IEEE.

Hlatky, M. A., Greenland, P., Arnett, D. K., Ballantyne, C. M., Criqui, M. H., Elkind, M. S., ... & Wilson, P. W. (2009). Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. *Circulation,* 119(17), 2408-2416.

Imam M. H., C. K. Karmakar, H. F. Jelinek, M. Palaniswami, ,A. H. Khandoker, "Analyzing systolic-diastolic interval interaction characteristics in diabetic cardiac autonomic neuropathy progression," *IEEE J. Transl. Eng. Heal. Med.,* vol. 3, 2015.

Jun, T. J., Nguyen, H. M., Kang, D., Kim, D., Kim, D., & Kim, Y. H. (2018). ECG arrhythmia classification using a 2-D convolutional neural network. *arXiv preprint arXiv:*1804.06812.

Kim, S. H., Lee, J. Y., Moon, S. S., Park, S. Y., & Lee, H. J. (2025). Cardiovascular autonomic neuropathy in long-standing diabetes: Clinical characteristics and risk factors. *Journal of Korean Medical Science,* 40, e154.

Liu, J., Tang, Z. H., Zeng, F., Li, Z., & Zhou, L. (2013). Artificial neural network models for prediction of cardiovascular autonomic dysfunction in general Chinese population. *BMC medical informatics and decision making,* 13(1), 80.

Nabrdalik, K., Irlik, K., Meng, Y., Nunes, A., Kuropka, P., Kania, M., ... & Gumprecht, J. (2024). Artificial intelligence-based classification of cardiac autonomic neuropathy from retinal fundus images: A cross-sectional study. *Cardiovascular Diabetology,* 23, Article 367.

Pappachan, J. M., Sebastian, J., Bino, B. C., Jayaprakash, K., Vijayakumar, K., Sujathan, P., & Adinegara, L. A. (2008). Cardiac autonomic neuropathy in diabetes mellitus: prevalence, risk factors and utility of corrected QT interval in the ECG for its diagnosis. *Postgraduate medical journal,* 84(990), 205-210.

Peura, R. A., & Webster, J. G. (2020). Basic sensors and principles. *Medical Instrumentation: application and design,* 91.

Raje, S., Maiya, G. A., D'Souza, R., & Nayak, A. (2025). Prediction of cardiac autonomic dysfunction using heart rate response to deep breathing test among type 2 diabetes mellitus: A cross-sectional study. *BMC Endocrine Disorders,* 25, 1939.

Senthamilselvan, S., Arjunan, S. P., Swaminathan, R., & Kumar, D. K. (2022). Complexity Analysis in the PR, QT, RR and ST Segments of ECG for Early Assessment of Severity in Cardiac Autonomic Neuropathy. *Applied Sciences,* 12(11), 5746.

Senthamilselvan, S., Maheshwari, M., Arjunan, S. P., Kumar, D. K., & Duggal, M. (2023, July). A translational study for detection of cardiac autonomic neuropathy using fractal features: A bench to bedside approach. In 2023 *45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)* (pp. 1-4). IEEE.

Serhiyenko, V. A., & Serhiyenko, A. A. (2018). Cardiac autonomic neuropathy: risk factors, diagnosis and treatment. *World journal of diabetes,* 9(1), 1.

Sharanya, S., & Arjunan, S. P. (2023). Fractal dimension techniques for analysis of cardiac autonomic neuropathy (CAN). *Biomedical Engineering: Applications, Basis and Communications,* 35(03), 2350003.

Sharanya, S., & Sridhar, P. A. (2021). A model for early diagnosis of Cardiac Autonomic Neuropathy (CAN). In *Journal of Physics: Conference Series* (Vol. 2089, No. 1, p. 012053). IOP Publishing.

Singh, R., Patel, A., & Varma, S. (2024). Identification of cardiac autonomic neuropathy progression using multifractal analysis of ECG signals. *Computing in Cardiology,* 51, 155.

Stern, S., & Sclarowsky, S. (2009). The ECG in diabetes mellitus. *Circulation,* 120(16), 1633-1636.